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(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING AN IMMUNE RESPONSE MODIFIER

(57) Abstract: Pharmaceutical formulations comprising an immune response modifier (IRM) chosen from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazolo-quinoline amines, oxazolo-quinolinamines, thiazolo-pyridinamines, oxazolo-pyridinamines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid are useful for the treatment of dermal associated conditions. Novel topical formulations are provided. In one embodiment, the topical formulations are advantageous for treatment of actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

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PHARMACEUTICAL FORMULATIONS COMPRISING AN IMMUNE RESPONSE MODIFIER

5

Field of the Invention

The present invention is directed to pharmaceutical formulations comprising at least one immune response modifier chosen from imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines. Embodiments of the present invention are directed to topical formulations for application to the skin of a mammal. Other embodiments of the present invention are directed to methods for treating dermal diseases.

Background

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, 1,2-bridged imidazoquinoline amine, thiazoloquinoline amine, oxazoloquinoline amine, thiazolopyridine amine, oxazolopyridine amine, imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, and thiazolonaphthyridine amine compounds have demonstrated potent immunostimulating, antiviral and antitumor (including anticancer) activity, and have also been shown to be useful as vaccine adjuvants. These compounds are hereinafter collectively referred to as "IRM" (immune response modifier) compounds. One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, Aldara™, for the treatment of anogenital warts associated with human papillomavirus.

The mechanism for the antiviral and antitumor activity of these IRM compounds is thought to be due in substantial part to enhancement of the immune response by induction of various important cytokines (e.g., interferons, interleukins, tumor necrosis factor, etc.). Such compounds have been shown to stimulate a rapid release of certain monocyte/macrophage-derived cytokines and are also capable of stimulating B cells to

secrete antibodies which play an important role in these IRM compounds' antiviral and antitumor activities. One of the predominant immunostimulating responses to these compounds is the induction of interferon (IFN)- α production, which is believed to be very important in the acute antiviral and antitumor activities seen. Moreover, up regulation of other cytokines such as, for example, tumor necrosis factor (TNF), Interleukin-1 (IL-1) and IL-6 also have potentially beneficial activities and are believed to contribute to the antiviral and antitumor properties of these compounds.

Although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM compound for treatment of a particular condition at a particular location may be hindered by a variety of factors. These factors include irritation of the skin to which the formulation is applied, formulation wash away, insolubility and/or degradation of the IRM compound in the formulation, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomeration of active ingredient, and the like), poor permeation, and undesired systemic delivery of the topically applied IRM compound. Accordingly, there is a continuing need for new methods and formulations to provide the greatest therapeutic benefit from this class of compounds.

Summary of the Invention

At several locations throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group; it is not meant that the list is exclusive.

In one aspect, the present invention is directed to a pharmaceutical formulation comprising an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

In one embodiment, the pharmaceutical formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

5 The formulation can further comprise one or more of a preservative system, an emulsifier, and water.

In another aspect, the present invention is directed to a method of treatment of a dermal associated condition comprising applying to skin a topical formulation comprising 10 an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine 15 amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carboomers.

20 In one embodiment, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

25 In other embodiments, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and further comprising one or more of a preservative system, an emulsifier, and water.

30 In one embodiment, the dermal associated condition is selected from actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

In another aspect, the present invention is directed to a method for delivering an immune response modifier to a dermal surface, the method comprising the steps of selecting a formulation comprising a compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazolo-quinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carboomers; and applying the selected formulation to the dermal surface for a time sufficient to allow the formulation to deliver the IRM to the dermal surface.

In one embodiment, the selected formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about".

As used herein, "a" or "an" or "the" are used interchangeably with "at least one", to mean "one or more" of the element being modified.

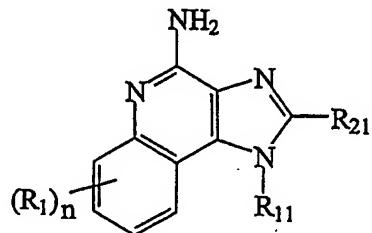
Detailed Description

In one aspect, the present invention is directed to a formulation comprising an immune response modifier compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component

miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms, and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carborimers.

These immune response modifier compounds, methods of making them, methods of using them and compositions containing them are disclosed in U.S. Patent Nos. 5 4,689,338; 4,929,624; 4,988,815; 5,037,986; 5,175,296; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,367,076; 5,389,640; 5,395,937; 5,446,153; 5,482,936; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,039,969; 6,083,505; 6,110,929; 6,194,425; 6,245,776; 6,331,539; 6,376,669; and 6,451,810; European Patent 0 394 026; US Publication 10 2002/0055517; and PCT Publications WO 00/47719; WO 00/76518; WO 01/74343; WO 02/46188; WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; WO 02/46194; and WO 02/46749 the disclosures of which are incorporated by reference herein.

As noted above, many of the IRM compounds useful in the present invention have demonstrated significant immunomodulating activity. In certain embodiments of the present invention, the IRM compound can be chosen from imidazoquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by one of Formulas I-V below:



I

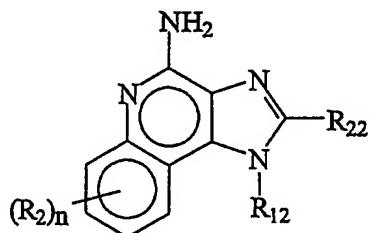
20 wherein

R₁₁ is chosen from alkyl of one to ten carbon atoms, hydroxyalkyl of one to six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen,

with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

R₂₁ is chosen from hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and

each R₁ is independently chosen from alkoxy of one to four carbon atoms, halogen, and alkyl of one to four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R₁ groups together contain no more than six carbon atoms;



II

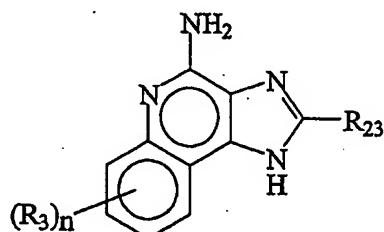
wherein

R₁₂ is chosen from straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from straight chain or branched chain alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

R₂₂ is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon

atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

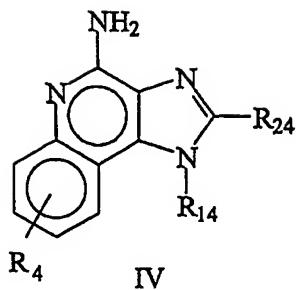
each R₂ is independently chosen from straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R₂ groups together contain no more than six carbon atoms;



wherein

R₂₃ is chosen from hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each R₃ is independently chosen from straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R₃ groups together contain no more than six carbon atoms;

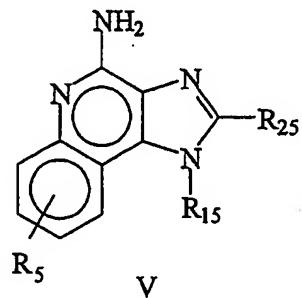


wherein

R₁₄ is -CHR_xR_y wherein R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuryl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms;

R₂₄ is chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

R₄ is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

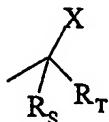


wherein

R₁₅ is chosen from: hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing

one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted
5 straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety
10 contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties
15 independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R₂₅ is



20 wherein

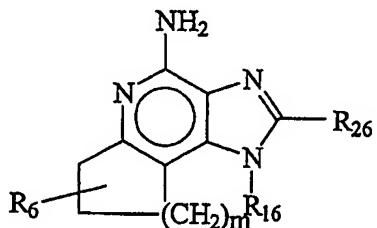
R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to four carbon atoms; and

R₅ is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

and a pharmaceutically acceptable salt of any of the foregoing.

The IRM compound can also be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:



VI

15

wherein m is 1, 2, or 3;

R₁₆ is chosen from hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six

carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

and -CHR_xR_y

wherein

R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuryl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms,

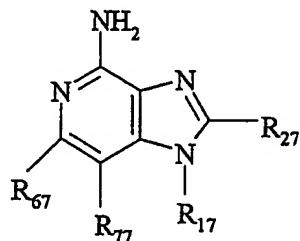
R₂₆ is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, morpholinoalkyl, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and

-C(R_S)(R_T)(X) wherein R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms, and

R₆ is chosen from hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom; and pharmaceutically acceptable salts thereof.

In other embodiments of the present invention, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:



VII

15

wherein

R₁₇ is chosen from hydrogen; -CH₂R_w wherein R_w is chosen from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and -CH=CR_zR_z wherein each R_z is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

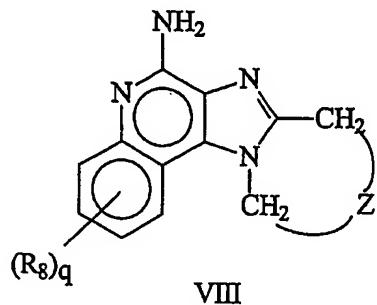
R₂₇ is chosen from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl,

the benzyl, (phenyl)ethyl and phenyl being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

R₆₇ and R₇₇ are independently chosen from hydrogen and alkyl of one to five carbon atoms, with the proviso that R₆₇ and R₇₇ taken together contain no more than six carbon atoms, and with the further proviso that when R₇₇ is hydrogen then R₆₇ is other than hydrogen and R₂₇ is other than hydrogen or morpholinoalkyl, and with the further proviso that when R₆₇ is hydrogen then R₇₇ and R₂₇ are other than hydrogen;

and pharmaceutically acceptable salts thereof.

In yet another embodiment of the present invention, the IRM compound can be chosen from 1,2-bridged imidazoquinoline amines defined by Formula VIII below:



wherein

Z is chosen from:

-(CH₂)_p- wherein p is 1 to 4;

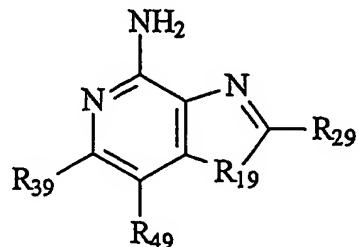
-(CH₂)_a-C(R_DR_E)(CH₂)_b-, wherein a and b are integers and a+b is 0 to 3, R_D is hydrogen or alkyl of one to four carbon atoms, and R_E is chosen from alkyl of one to four carbon atoms, hydroxy, -OR_F wherein R_F is alkyl of one to four carbon atoms, and -NR_GR'_G wherein R_G and R'_G are independently hydrogen or alkyl of one to four carbon atoms; and

-(CH₂)_a-(Y)-(CH₂)_b- wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or -NR_J- wherein R_J is hydrogen or alkyl of one to four carbon atoms;

and wherein q is 0 or 1 and R₈ is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,

and pharmaceutically acceptable salts thereof.

In a further embodiment, the IRM compound can be chosen from thiazoloquinoline amines, oxazoloquinoline amines, thiazolonaphthyridine amines, thiazolopyridine amines, and oxazolopyridine amines of Formula IX:



IX

5

wherein:

R₁₉ is chosen from oxygen, sulfur and selenium;

R₂₉ is chosen from

- 10 -hydrogen;
- alkyl;
- alkyl-OH;
- haloalkyl;
- alkenyl;
- 15 -alkyl-X-alkyl;
- alkyl-X-alkenyl;
- alkenyl-X-alkyl;
- alkenyl-X-alkenyl;
- alkyl-N(R₅₉)₂;
- 20 -alkyl-N₃;
- alkyl-O-C(O)-N(R₅₉)₂;
- heterocyclyl;
- alkyl-X-heterocyclyl;
- alkenyl-X-heterocyclyl;
- 25 -aryl;
- alkyl-X-aryl;

-alkenyl-X-aryl;
 -heteroaryl;
 -alkyl-X-heteroaryl; and
 -alkenyl-X-heteroaryl;

5 R_{39} and R_{49} are each independently:

-hydrogen;
 -X-alkyl;
 -halo;
 -haloalkyl;
 - $N(R_{59})_2$;

10 or when taken together, R_{39} and R_{49} form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

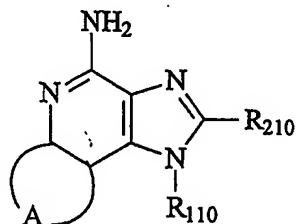
X is chosen from $-O-$, $-S-$, $-NR_{59}-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, and a bond;

and

15 each R_{59} is independently H or C_{1-8} alkyl;
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines of Formulae X and XI below:

20



X

wherein

A is $=N-CR=CR-CR=;$; $=CR-N=CR-CR=;$; $=CR-CR=N-CR=;$ or
 $=CR-CR=CR-N=;$

25 R_{110} is chosen from:

- hydrogen;

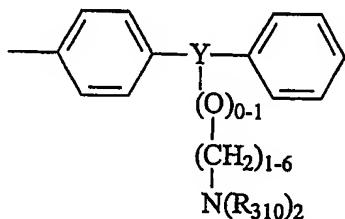
-C₁₋₂₀ alkyl or C₂₋₂₀ alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

- aryl;
- heteroaryl;
- heterocyclyl;
- O-C₁₋₂₀ alkyl,
- O-(C₁₋₂₀ alkyl)₀₋₁-aryl;
- O-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
- O-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
- CO-O-C₁₋₂₀ alkyl;
- S(O)₀₋₂-C₁₋₂₀ alkyl;
- S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-aryl;
- S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
- S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
- N(R₃₁₀)₂;
- N₃;
- oxo;
- halogen;
- NO₂;
- OH; and
- SH; and

-C₁₋₂₀ alkyl-NR₃₁₀-Q-X-R₄₁₀ or -C₂₋₂₀ alkenyl-NR₃₁₀-Q-X-R₄₁₀ wherein Q is -CO- or -SO₂-; X is a bond, -O- or -NR₃₁₀- and R₄₁₀ is aryl; heteroaryl; heterocyclyl; or -C₁₋₂₀ alkyl or C₂₋₂₀ alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

- aryl;
- heteroaryl;
- heterocyclyl;
- O-C₁₋₂₀ alkyl,
- O-(C₁₋₂₀ alkyl)₀₋₁-aryl;
- O-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
- O-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;

-CO-O-C₁₋₂₀ alkyl;
- $S(O)_{0-2}$ -C₁₋₂₀ alkyl;
- $S(O)_{0-2}$ -(C₁₋₂₀ alkyl)₀₋₁-aryl;
- $S(O)_{0-2}$ -(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
5 - $S(O)_{0-2}$ -(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
-N(R₃₁₀)₂;
-NR₃₁₀-CO-O-C₁₋₂₀ alkyl;
-N₃;
oxo;
10 -halogen;
-NO₂;
-OH; and
-SH; or R₄₁₀ is



15

wherein Y is -N- or -CR-;

R₂₁₀ is chosen from:

-hydrogen;
-C₁₋₁₀ alkyl;
20 -C₂₋₁₀ alkenyl;
-aryl;
-C₁₋₁₀ alkyl-O-C₁₋₁₀ alkyl;
-C₁₋₁₀ alkyl-O-C₂₋₁₀ alkenyl; and
-C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl substituted by one or more substituents chosen from:
25 -OH;
-halogen;
-N(R₃₁₀)₂;
-CO-N(R₃₁₀)₂;

-CO-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-heteroaryl;

5 -heterocycll;

-CO-aryl; and

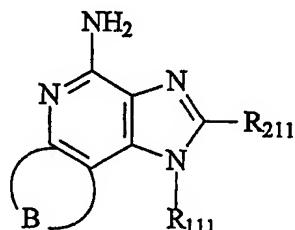
-CO-heteroaryl;

each R₃₁₀ is independently chosen from hydrogen and C₁₋₁₀ alkyl; and

each R is independently chosen from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halogen

10 and trifluoromethyl,

and pharmaceutically acceptable salts thereof;



XI

15 wherein

B is -NR-C(R)₂-C(R)₂-C(R)₂-; -C(R)₂-NR-C(R)₂-C(R)₂-;
-C(R)₂-C(R)₂-NR-C(R)₂- or -C(R)₂-C(R)₂-C(R)₂-NR-;

R₁₁₁ is chosen from:

- hydrogen;

20 -C₁₋₂₀ alkyl or C₂₋₂₀ alkenyl that is unsubstituted or substituted by one or more
substituents chosen from:

-aryl;

-heteroaryl;

-heterocycll;

-O-C₁₋₂₀ alkyl;

-O-(C₁₋₂₀ alkyl)₀₋₁-aryl;

-O-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;

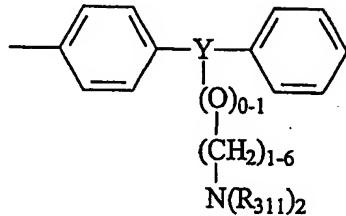
25

-O-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
-CO-O-C₁₋₂₀ alkyl;
-S(O)₀₋₂-C₁₋₂₀ alkyl;
-S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-aryl;
5 -S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
-S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
-N(R₃₁₁)₂;
-N₃;
oxo;
10 -halogen;
-NO₂;
-OH; and
-SH; and

-C₁₋₂₀ alkyl-NR₃₁₁-Q-X-R₄₁₁ or -C₂₋₂₀ alkenyl-NR₃₁₁-Q-X-R₄₁₁ wherein Q is -CO-
15 or -SO₂-; X is a bond, -O- or -NR₃₁₁- and R₄₁₁ is aryl; heteroaryl; heterocyclyl; or -C₁₋₂₀
alkyl or C₂₋₂₀ alkenyl that is unsubstituted or substituted by one or more substituents
chosen from:

20 -aryl;
-heteroaryl;
-heterocyclyl;
-O-C₁₋₂₀ alkyl,
-O-(C₁₋₂₀ alkyl)₀₋₁-aryl;
-O-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
-O-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
25 -CO-O-C₁₋₂₀ alkyl;
-S(O)₀₋₂-C₁₋₂₀ alkyl;
-S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-aryl;
-S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heteroaryl;
-S(O)₀₋₂-(C₁₋₂₀ alkyl)₀₋₁-heterocyclyl;
30 -N(R₃₁₁)₂;
-NR₃₁₁-CO-O-C₁₋₂₀ alkyl;
-N₃;

oxo;
 -halogen;
 -NO₂;
 -OH; and
 5 -SH; or R₄₁₁ is



wherein Y is -N- or -CR-;

R₂₁₁ is chosen from:

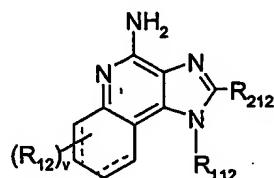
- hydrogen;
- 10 -C₁₋₁₀ alkyl;
- C₂₋₁₀ alkenyl;
- aryl
- C₁₋₁₀ alkyl -O-C₁₋₁₀-alkyl;
- C₁₋₁₀ alkyl-O-C₂₋₁₀ alkenyl; and
- 15 -C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl substituted by one or more substituents chosen from:
 - OH;
 - halogen;
 - N(R₃₁₁)₂;
 - CO-N(R₃₁₁)₂;
 - 20 -CO-C₁₋₁₀ alkyl;
 - N₃;
 - aryl;
 - heteroaryl;
 - heterocycl;
 - 25 -CO-aryl; and
 - CO-heteroaryl;

each R₃₁₁ is independently chosen from hydrogen and C₁₋₁₀ alkyl; and

each R is independently chosen from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halogen and trifluoromethyl,

and pharmaceutically acceptable salts thereof.

In a further embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XII, XIII and XIV below:



XII

10

wherein

R₁₁₂ is -alkyl-NR₃₁₂-CO-R₄₁₂ or -alkenyl-NR₃₁₂-CO- R₄₁₂ wherein R₄₁₂ is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

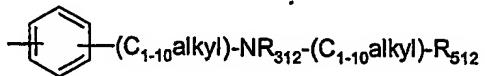
15

- alkyl;
- alkenyl;
- alkynyl;
- (alkyl)₀₋₁-aryl;
- (alkyl)₀₋₁-(substituted aryl);
- (alkyl)₀₋₁-heteroaryl;
- (alkyl)₀₋₁-(substituted heteroaryl);
- O-alkyl;
- O-(alkyl)₀₋₁-aryl;
- O-(alkyl)₀₋₁-(substituted aryl);
- O-(alkyl)₀₋₁-heteroaryl;
- O-(alkyl)₀₋₁-(substituted heteroaryl);
- CO-aryl;
- CO-(substituted aryl);

20

25

-CO-heteroaryl;
 -CO-(substituted heteroaryl);
 -COOH;
 -CO-O-alkyl;
 5 -CO-alkyl;
 -S(O)₀₋₂-alkyl;
 -S(O)₀₋₂-(alkyl)₀₋₁-aryl;
 -S(O)₀₋₂-(alkyl)₀₋₁-(substituted aryl);
 -S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
 10 -S(O)₀₋₂-(alkyl)₀₋₁-(substituted heteroaryl);
 -P(O)(OR₃₁₂)₂;
 -NR₃₁₂-CO-O-alkyl;
 -N₃;
 -halogen;
 15 -NO₂;
 -CN;
 -haloalkyl;
 -O-haloalkyl;
 -CO-haloalkyl;
 20 -OH;
 -SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;
 or R₄₁₂ is



25 wherein R₅₁₂ is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl), heterocyclyl or (substituted heterocyclyl) group;

R₂₁₂ is chosen from:

-hydrogen;
 -alkyl;
 30 -alkenyl;
 -aryl;

- (substituted aryl);
- heteroaryl;
- (substituted heteroaryl);
- heterocyclyl;
5 - (substituted heterocyclyl);
- alkyl-O-alkyl;
- alkyl-O-alkenyl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:
- OH;
10 - halogen;
- N(R₃₁₂)₂;
- CO-N(R₃₁₂)₂;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
15 - N₃;
- aryl;
- (substituted aryl);
- heteroaryl;
- (substituted heteroaryl);
20 - heterocyclyl;
- (substituted heterocyclyl);
- CO-aryl; and
- CO-heteroaryl;

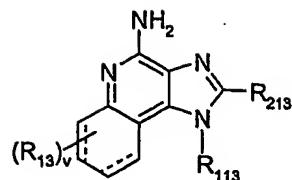
each R₃₁₂ is independently chosen from hydrogen; C₁₋₁₀ alkyl-heteroaryl; C₁₋₁₀

25 alkyl-(substituted heteroaryl); C₁₋₁₀ alkyl-aryl; C₁₋₁₀ alkyl-(substituted aryl) and C₁₋₁₀ alkyl;

v is 0 to 4;

and each R₁₂ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy,
halogen and trifluoromethyl;

30



wherein

R_{113} is -alkyl-N R_{313} -SO₂-X-R₄₁₃ or -alkenyl-N R_{313} -SO₂-X-R₄₁₃;

5 X is a bond or -NR₅₁₃-;

R_{413} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

-alkyl;

-alkenyl;

10 -aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

15 -substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)₀₋₁-aryl;

-O-(alkyl)₀₋₁-substituted aryl;

20 -O-(alkyl)₀₋₁-heteroaryl;

-O-(alkyl)₀₋₁-substituted heteroaryl;

-O-(alkyl)₀₋₁-heterocyclyl;

-O-(alkyl)₀₋₁-substituted heterocyclyl;

-COOH;

25 -CO-O-alkyl;

-CO-alkyl;

-S(O)₀₋₂-alkyl;

-S(O)₀₋₂-(alkyl)₀₋₁-aryl;

- S(O)₀₋₂-(alkyl)₀₋₁-substituted aryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted heteroaryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
 - 5 -S(O)₀₋₂-(alkyl)₀₋₁-substituted heterocyclyl;
 - (alkyl)₀₋₁-NR₃₁₃R₃₁₃;
 - (alkyl)₀₋₁-NR₃₁₃-CO-O-alkyl;
 - (alkyl)₀₋₁-NR₃₁₃-CO-alkyl;
 - (alkyl)₀₋₁-NR₃₁₃-CO-aryl;
 - 10 -(alkyl)₀₋₁-NR₃₁₃-CO-substituted aryl;
 - (alkyl)₀₋₁-NR₃₁₃-CO-heteroaryl;
 - (alkyl)₀₋₁-NR₃₁₃-CO-substituted heteroaryl;
 - N₃;
 - 15 -halogen;
 - haloalkyl;
 - haloalkoxy;
 - CO-haloalkyl;
 - CO-haloalkoxy;
 - NO₂;
 - 20 -CN;
 - OH;
 - SH; and in the case that R₄₁₃ is alkyl, alkenyl, or heterocyclyl, oxo;
- R₂₁₃ is chosen from:
- hydrogen;
 - 25 -alkyl;
 - alkenyl;
 - aryl;
 - substituted aryl;
 - heteroaryl;
 - 30 -substituted heteroaryl;
 - alkyl-O-alkyl;
 - alkyl-O- alkenyl; and

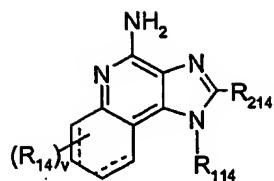
- alkyl or alkenyl substituted by one or more substituents chosen from:

- OH;
- halogen;
- N(R₃₁₃)₂;
- 5 -CO-N(R₃₁₃)₂;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
- N₃;
- aryl;
- 10 -substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- heterocyclyl;
- substituted heterocyclyl;
- 15 -CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl; and
- CO-(substituted heteroaryl);

each R₃₁₃ is independently chosen from hydrogen, C₁₋₁₀ alkyl, and when X is a bond R₃₁₃ and R₄₁₃ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

R₅₁₃ is chosen from hydrogen, C₁₋₁₀ alkyl, and R₄₁₃ and R₅₁₃ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4 and each R₁₃ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halogen and trifluoromethyl;



XIV

wherein

5 **R**₁₁₄ is -alkyl-NR₃₁₄-CY-NR₅₁₄-X-R₄₁₄ or -alkenyl-NR₃₁₄-CY- NR₅₁₄-X- R₄₁₄

wherein

Y is =O or =S;

X is a bond, -CO- or -SO₂-;

10 **R**₄₁₄ is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be

unsubstituted or substituted by one or more substituents chosen from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

15 -heterocyclyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

20 -O-(alkyl)₀₋₁-aryl;

-O-(alkyl)₀₋₁-substituted aryl;

-O-(alkyl)₀₋₁-heteroaryl;

-O-(alkyl)₀₋₁-substituted heteroaryl;

-O-(alkyl)₀₋₁-heterocyclyl;

25 -O-(alkyl)₀₋₁-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)₀₋₂-alkyl;
 -S(O)₀₋₂-(alkyl)₀₋₁-aryl;
 -S(O)₀₋₂-(alkyl)₀₋₁-substituted aryl;
 -S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
 5 -S(O)₀₋₂-(alkyl)₀₋₁-substituted heteroaryl;
 -S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
 -S(O)₀₋₂-(alkyl)₀₋₁-substituted heterocyclyl;
 -(alkyl)₀₋₁-NR₃₁₄R₃₁₄;
 - (alkyl)₀₋₁-NR₃₁₄-CO-O-alkyl;
 10 -(alkyl)₀₋₁-NR₃₁₄-CO-alkyl;
 -(alkyl)₀₋₁-NR₃₁₄-CO-aryl;
 -(alkyl)₀₋₁-NR₃₁₄-CO-substituted aryl;
 -(alkyl)₀₋₁-NR₃₁₄-CO-heteroaryl;
 - (alkyl)₀₋₁-NR₃₁₄-CO-substituted heteroaryl;
 15 -N₃;
 -halogen;
 -haloalkyl;
 -haloalkoxy;
 -CO-haloalkoxy;
 20 -NO₂;
 -CN;
 -OH;
 -SH; and, in the case that R₄₁₄ is alkyl, alkenyl or heterocyclyl, oxo;
 with the proviso that when X is a bond R₄₁₄ can additionally be hydrogen;
 25 R₂₁₄ is chosen from:
 -hydrogen;
 -alkyl;
 -alkenyl;
 -aryl;
 30 -substituted aryl;
 -heteroaryl;
 -substituted heteroaryl;

- alkyl -O-alkyl;
-alkyl-O- alkenyl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:

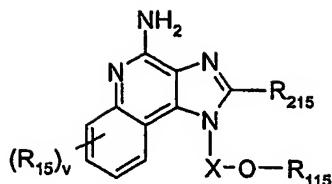
5 -OH;
-halogen;
-N(R₃₁₄)₂;
-CO-N(R₃₁₄)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
10 -N₃;
-aryl;
-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
15 -heterocycli;
-substituted heterocycli;
-CO-aryl;
-CO-(substituted aryl);
-CO-heteroaryl; and
20 -CO-(substituted heteroaryl);

each R₃₁₄ is independently chosen from hydrogen and C₁₋₁₀ alkyl;

R₅₁₄ is chosen from hydrogen, C₁₋₁₀ alkyl, and R₄₁₄ and R₅₁₄ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4 and each R₁₄ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halogen and trifluoromethyl,
25 and pharmaceutically acceptable salts thereof.

In yet another embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, 30 and XXVI below



XV

5

wherein: **X** is -CHR₅₁₅-, -CH₂R₅₁₅-alkyl-, or -CH₂R₅₁₅-alkenyl-;

10

R₁₁₅ is chosen from:

- R₄₁₅-CR₃₁₅-Z-R₆₁₅-alkyl;
- R₄₁₅-CR₃₁₅-Z-R₆₁₅-alkenyl;
- R₄₁₅-CR₃₁₅-Z-R₆₁₅-aryl;
- R₄₁₅-CR₃₁₅-Z-R₆₁₅-heteroaryl;
- R₄₁₅-CR₃₁₅-Z-R₆₁₅-heterocyclyl;
- R₄₁₅-CR₃₁₅-Z-H;
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₆₁₅-alkyl;
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₆₁₅-alkenyl;
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₆₁₅-aryl;
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₆₁₅-heteroaryl;
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₆₁₅-heterocyclyl; and
- R₄₁₅-NR₇₁₅-CR₃₁₅-R₈₁₅;

15

20

Z is -NR₅₁₅-, -O-, or -S-;

25

R₂₁₅ is chosen from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

30

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;
-halogen;
-N(R₅₁₅)₂;
-CO-N(R₅₁₅)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
-N₃;
-aryl;
-heteroaryl;
-heterocycll;
-CO-aryl; and
-CO-heteroaryl;

5

10

15

20

25

R₃₁₅ is =O or =S;

R₄₁₅ is alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R₅₁₅ is independently H or C₁₋₁₀ alkyl;

R₆₁₅ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R₇₁₅ is H, C₁₋₁₀ alkyl, arylalkyl, or R₄₁₅ and R₇₁₅ can join together to form a 5 to 7 membered heterocyclic ring;

R₈₁₅ is H, C₁₋₁₀ alkyl, or R₇₁₅ and R₈₁₅ can join together to form a 5 to 7 membered heterocyclic ring;

Y is -O- or -S(O)₀₋₂;

v is 0 to 4; and

each R₁₅ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;



XVI

wherein: **X** is $-\text{CHR}_{516}-$, $-\text{CHR}_{516}\text{-alkyl}$, or $-\text{CHR}_{516}\text{-alkenyl}$;

5 **R₁₁₆** is chosen from:

- R₄₁₆-CR₃₁₆-Z-R₆₁₆-alkyl;
- R₄₁₆-CR₃₁₆-Z-R₆₁₆-alkenyl;
- R₄₁₆-CR₃₁₆-Z-R₆₁₆-aryl;
- R₄₁₆-CR₃₁₆-Z-R₆₁₆-heteroaryl;
- 10 -R₄₁₆-CR₃₁₆-Z-R₆₁₆-heterocyclyl;
- R₄₁₆-CR₃₁₆-Z-H;
- R₄₁₆-NR₇₁₆-CR₃₁₆-R₆₁₆-alkyl;
- R₄₁₆-NR₇₁₆-CR₃₁₆-R₆₁₆-alkenyl;
- R₄₁₆-NR₇₁₆-CR₃₁₆-R₆₁₆-aryl;
- 15 -R₄₁₆-NR₇₁₆-CR₃₁₆-R₆₁₆-heteroaryl;
- R₄₁₆-NR₇₁₆-CR₃₁₆-R₆₁₆-heterocyclyl; and
- R₄₁₆-NR₇₁₆-CR₃₁₆-R₈₁₆;

Z is $-\text{NR}_{516}-$, $-\text{O}-$, or $-\text{S}-$;

R₂₁₆ is chosen from:

- 20 -hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- 25 -heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

- OH;
- halogen;
- N(R₅₁₆)₂;
- CO-N(R₅₁₆)₂;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
- N₃;
- aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

10

R₃₁₆ is =O or =S;

R₄₁₆ is alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R₅₁₆ is independently H or C₁₋₁₀ alkyl;

R₆₁₆ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R₇₁₆ is H, C₁₋₁₀ alkyl, arylalkyl, or R₄₁₆ and R₇₁₆ can join together to form a 5 to 7 membered heterocyclic ring;

R₈₁₆ is H or C₁₋₁₀ alkyl; or R₇₁₆ and R₈₁₆ can join together to form a 5 to 7 membered heterocyclic ring;

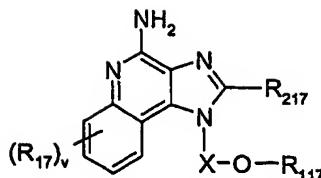
Y is -O- or -S(O)₀₋₂₋;

v is 0 to 4; and

each R₁₆ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen, and trifluoromethyl;

20

25



wherein: **X** is $-\text{CHR}_{317}-$, $-\text{CHR}_{317}\text{-alkyl}$, or $-\text{CHR}_{317}\text{-alkenyl}$;

R₁₁₇ is chosen from:

-alkenyl;

-aryl; and

$-\text{R}_{417}\text{-aryl}$;

R₂₁₇ is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen

from:

$-\text{OH}$;

-halogen;

$-\text{N}(\text{R}_{317})_2$;

$-\text{CO-N}(\text{R}_{317})_2$;

25 $-\text{CO-C}_{1-10}\text{ alkyl}$;

$-\text{CO-O-C}_{1-10}\text{ alkyl}$;

$-\text{N}_3$;

-aryl;

-heteroaryl;

-heterocyclyl;
 -CO-aryl; and
 -CO-heteroaryl;

R₄₁₇ is alkyl or alkenyl, which may be interrupted by one or more

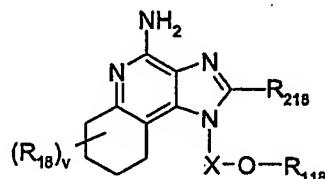
5 -O— groups;

each **R₃₁₇** is independently H or C₁₋₁₀ alkyl;

each Y is independently —O— or —S(O)₀₋₂—;

v is 0 to 4; and

each **R₁₇** present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy,
 10 hydroxy, halogen and trifluoromethyl;



XVIII

15 wherein: X is —CHR₃₁₈—, —CHR₃₁₈-alkyl-, or —CHR₃₁₈-alkenyl-;

R₁₁₈ is chosen from:

-aryl;
 -alkenyl; and
 -R₄₁₈-aryl;

R₂₁₈ is chosen from:

-hydrogen;
 -alkyl;
 -alkenyl;
 -aryl;
 -heteroaryl;
 -heterocyclyl;
 -alkyl-Y-alkyl;
 -alkyl-Y-aryl;
 -alkyl-Y- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

- OH;
- halogen;
- N(R₃₁₈)₂;
- CO-N(R₃₁₈)₂;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
- N₃;
- aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

5

10

15

20

25

R₄₁₈ is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

each R₃₁₈ is independently H or C₁₋₁₀ alkyl;

each Y is independently -O- or -S(O)₀₋₂₋;

v is 0 to 4; and

each R₁₈ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;



XIX

wherein: X is -CHR₃₁₉-, -CHR₃₁₉-alkyl-, or -CHR₃₁₉-alkenyl-;

R₁₁₉ is chosen from:

- heteroaryl;
- heterocyclyl;

-R₄₁₉- heteroaryl; and

-R₄₁₉- heterocyclyl;

R₂₁₉ is chosen from:

-hydrogen;

5 -alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

10 -alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen
from:

15 -OH;

-halogen;

-N(R₃₁₉)₂;

-CO-N(R₃₁₉)₂;

-CO-C₁₋₁₀ alkyl;

20 -CO-O-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-heteroaryl;

-heterocyclyl;

25 -CO-aryl; and

-CO-heteroaryl;

R₄₁₉ is alkyl or alkenyl, which may be interrupted by one or more

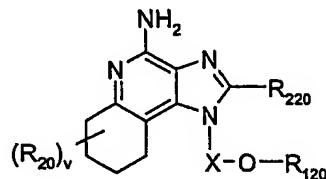
-O- groups;

each R₃₁₉ is independently H or C₁₋₁₀ alkyl;

30 each Y is independently -O- or -S(O)₀₋₂₋;

v is 0 to 4; and

each R_{19} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XX

5

wherein: X is $-CHR_{320}-$, $-CHR_{320}-alkyl-$, or $-CHR_{320}-alkenyl-$;

R_{120} is chosen from:

- heteroaryl;
- heterocyclyl;
- $-R_{420}-$ heteroaryl; and
- $-R_{420}-$ heterocyclyl;

R_{220} is chosen from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:
 - OH;
 - halogen;
 - $-N(R_{320})_2$;
 - $-CO-N(R_{320})_2$;
 - $-CO-C_{1-10}$ alkyl;

-CO-O-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

5

R₄₂₀ is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

10

each R₃₂₀ is independently H or C₁₋₁₀ alkyl;

each Y is independently -O- or -S(O)₀₋₂-;

v is 0 to 4; and

each R₂₀ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;

15



wherein: X is -CHR₅₂₁-, -CH₂R₅₂₁-alkyl-, or -CH₂R₅₂₁-alkenyl-;

20

R₁₂₁ is chosen from:

-R₄₂₁-NR₃₂₁-SO₂-R₆₂₁-alkyl;

-R₄₂₁-NR₃₂₁-SO₂-R₆₂₁-alkenyl;

-R₄₂₁-NR₃₂₁-SO₂-R₆₂₁-aryl;

-R₄₂₁-NR₃₂₁-SO₂-R₆₂₁-heteroaryl;

-R₄₂₁-NR₃₂₁-SO₂-R₆₂₁-heterocyclyl;

-R₄₂₁-NR₃₂₁-SO₂-R₇₂₁;

-R₄₂₁-NR₃₂₁-SO₂-NR₅₂₁-R₆₂₁-alkyl;

-R₄₂₁-NR₃₂₁-SO₂-NR₅₂₁-R₆₂₁-alkenyl;

-R₄₂₁-NR₃₂₁-SO₂-NR₅₂₁-R₆₂₁-aryl;

25

-R₄₂₁-NR₃₂₁-SO₂-NR₅₂₁-R₆₂₁-heteroaryl;
-R₄₂₁-NR₃₂₁-SO₂-NR₅₂₁-R₆₂₁-heterocyclyl; and
-R₄₂₁-NR₃₂₁-SO₂-NH₂;

R₂₂₁ is chosen from:

5

-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
10 -heterocyclyl;
-alkyl-Y-alkyl;
-alkyl-Y- alkenyl;
-alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen
15 from:
-OH;
-halogen;
-N(R₅₂₁)₂;

-CO-N(R₅₂₁)₂;

20

-CO-C₁₋₁₀ alkyl;

-CO-O-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-heteroaryl;

25

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

Y is -O- or -S(O)₀₋₂₋;

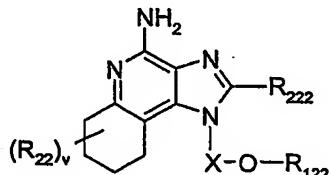
R₃₂₁ is H, C₁₋₁₀ alkyl, or arylalkyl;

30

each R₄₂₁ is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups, or R₃₂₁ and R₄₂₁ can join together to form a 5 to 7 membered heterocyclic ring;

each R_{521} is independently H, C₁₋₁₀ alkyl, or C₂₋₁₀ alkenyl;
R₆₂₁ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;
R₇₂₁ is C₁₋₁₀ alkyl, or R₃₂₁ and R₇₂₁ can join together to form a 5 to 7 membered heterocyclic ring;
5 **v** is 0 to 4; and
each R₂₁ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;

10



XXII

wherein: **X** is -CHR₅₂₂-, -CHR₅₂₂-alkyl-, or -CHR₅₂₂-alkenyl-;
R₁₂₂ is chosen from:

15

- R₄₂₂-NR₃₂₂-SO₂-R₆₂₂-alkyl;

- R₄₂₂-NR₃₂₂-SO₂-R₆₂₂-alkenyl;

- R₄₂₂-NR₃₂₂-SO₂-R₆₂₂-aryl;

- R₄₂₂-NR₃₂₂-SO₂-R₆₂₂-heteroaryl;

- R₄₂₂-NR₃₂₂-SO₂-R₆₂₂-heterocyclyl;

- R₄₂₂-NR₃₂₂-SO₂-R₇₂₂;

- R₄₂₂-NR₃₂₂-SO₂-NR₅₂₂-R₆₂₂-alkyl;

- R₄₂₂-NR₃₂₂-SO₂-NR₅₂₂-R₆₂₂-alkenyl;

- R₄₂₂-NR₃₂₂-SO₂-NR₅₂₂-R₆₂₂-aryl;

- R₄₂₂-NR₃₂₂-SO₂-NR₅₂₂-R₆₂₂-heteroaryl;

20

- R₄₂₂-NR₃₂₂-SO₂-NR₅₂₂-R₆₂₂-heterocyclyl; and

- R₄₂₂-NR₃₂₂-SO₂-NH₂;

R₂₂₂ is chosen from:

- hydrogen;

- alkyl;

-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-alkyl-Y-alkyl;
-alkyl-Y- alkenyl;
-alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen
from:

10 -OH;
-halogen;
-N(R₅₂₂)₂;
-CO-N(R₅₂₂)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
15 -N₃;
-aryl;
-heteroaryl;
-heterocyclyl;
20 -CO-aryl; and
-CO-heteroaryl;

Y is -O- or -S(O)₀₋₂₋;

R₃₂₂ is H, C₁₋₁₀ alkyl, or arylalkyl;

each R₄₂₂ is independently alkyl or alkenyl, which may be interrupted by
one or more -O- groups, or R₃₂₂ and R₄₂₂ can join together to form a 5 to 7
membered heterocyclic ring;

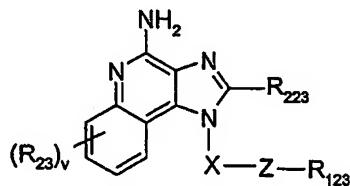
each R₅₂₂ is independently H, C₁₋₁₀ alkyl, or C₂₋₁₀ alkenyl;

R₆₂₂ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -
O- groups;

30 R₇₂₂ is C₁₋₁₀ alkyl, or R₃₂₂ and R₇₂₂ can join together to form a 5 to 7
membered heterocyclic ring;

v is 0 to 4; and

each R_{22} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;



5

wherein: X is $-CHR_{323}-$, $-CHR_{323}-alkyl-$, or $-CHR_{323}-alkenyl-$;

Z is $-S-$, $-SO-$, or $-SO_2-$;

R_{123} is chosen from:

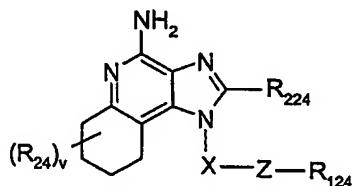
- 10 -alkyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkenyl;
- 15 -R₄₂₃-aryl;
- R₄₂₃- heteroaryl;
- R₄₂₃-heterocyclyl;

R_{223} is chosen from:

- 20 -hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- 25 -alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;
 -halogen;
 -N(R₃₂₃)₂;
 -CO-N(R₃₂₃)₂;
 5 -CO-C₁₋₁₀ alkyl;
 -CO-O-C₁₋₁₀ alkyl;
 -N₃;
 -aryl;
 -heteroaryl;
 10 -heterocyclyl;
 -CO-aryl; and
 -CO-heteroaryl;

each R₃₂₃ is independently H or C₁₋₁₀ alkyl;
 each R₄₂₃ is independently alkyl or alkenyl;
 15 each Y is independently -O- or -S(O)₀₋₂₋;
 v is 0 to 4; and
 each R₂₃ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy,
 hydroxy, halogen and trifluoromethyl;



20

XXIV

wherein: X is -CHR₃₂₄-, -CHR₃₂₄-alkyl-, or -CHR₃₂₄-alkenyl-;
 Z is -S-, -SO-, or -SO₂-;

25

R₁₂₄ is chosen from:

- alkyl;
- aryl;
- heteroaryl;
- heterocyclyl;

-alkenyl;
-R₄₂₄-aryl;
-R₄₂₄-heteroaryl; and
-R₄₂₄-heterocyclyl;

5 R₂₂₄ is chosen from:

-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
-alkyl-Y-aryl; and

10 15 - alkyl or alkenyl substituted by one or more substituent chosen from:

-OH;
-halogen;
-N(R₃₂₄)₂;
-CO-N(R₃₂₄)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
-N₃;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

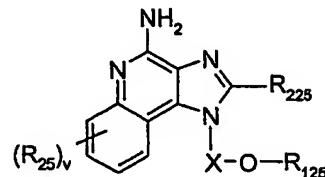
25 each R₃₂₄ is independently H or C₁₋₁₀ alkyl;

30 each R₄₂₄ is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)₀₋₂-;

v is 0 to 4; and

each R_{24} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



5

XXV

wherein: X is $-CHR_{525}-$, $-CHR_{525}-alkyl-$, or $-CHR_{525}-alkenyl-$;
 R_{125} is chosen from:

- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-alkyl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-alkenyl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-aryl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-heteroaryl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-heterocyclyl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}R_{725};$
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-alkyl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-alkenyl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-aryl;$
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-heteroaryl; and$
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-heterocyclyl;$

15

R_{225} is chosen from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and

20

- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;
-halogen;
-N(R₅₂₅)₂;
-CO-N(R₅₂₅)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
-N₃;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

15 each R₃₂₅ is =O or =S;

each R₄₂₅ is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R₅₂₅ is independently H or C₁₋₁₀ alkyl;

R₆₂₅ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R₇₂₅ is H, C₁₋₁₀ alkyl which may be interrupted by a hetero atom, or R₇₂₅ can join with R₅₂₅ to form a 5 to 7 membered heterocyclic ring;

R₈₂₅ is H, C₁₋₁₀ alkyl, arylalkyl, or R₄₂₅ and R₈₂₅ can join together to form a 5 to 7 membered heterocyclic ring;

25 R₉₂₅ is C₁₋₁₀ alkyl which can join together with R₈₂₅ to form a 5 to 7 membered heterocyclic ring;

each Y is independently -O- or -S(O)₀₋₂-;

Z is a bond, -CO-, or -SO₂-;

v is 0 to 4; and

30 each R₂₅ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;



XXVI

wherein: **X** is -CHR₅₂₆-; -CH₂R₅₂₆-alkyl-; or -CH₂R₅₂₆-alkenyl-;

R₁₂₆ is chosen from:

- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆-Z-R₆₂₆-alkyl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆-Z-R₆₂₆-alkenyl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆-Z-R₆₂₆-aryl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆-Z-R₆₂₆-heteroaryl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆-Z-R₆₂₆-heterocycl1;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₅₂₆R₇₂₆;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₉₂₆-Z-R₆₂₆-alkyl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₉₂₆-Z-R₆₂₆-alkenyl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₉₂₆-Z-R₆₂₆-aryl;
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₉₂₆-Z-R₆₂₆-heteroaryl; and
- R₄₂₆-NR₈₂₆-CR₃₂₆-NR₉₂₆-Z-R₆₂₆-heterocycl1;

R₂₂₆ is chosen from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocycl1;
- alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:
 - OH;

-halogen;
-N(R₅₂₆)₂;
-CO-N(R₅₂₆)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
5 -N₃;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

10

each R₃₂₆ is =O or =S;

each R₄₂₆ is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

15

each R₅₂₆ is independently H or C₁₋₁₀ alkyl;

R₆₂₆ is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R₇₂₆ is H, C₁₋₁₀ alkyl which may be interrupted by a hetero atom, or R₇₂₆ can join with R₅₂₆ to form a 5 to 7 membered heterocyclic ring;

20

R₈₂₆ is H, C₁₋₁₀ alkyl, arylalkyl, or R₄₂₆ and R₈₂₆ can join together to form a 5 to 7 membered heterocyclic ring;

R₉₂₆ is C₁₋₁₀ alkyl which can join together with R₈₂₆ to form a 5 to 7 membered heterocyclic ring;

each Y is independently -O- or -S(O)₀₋₂-;

25

Z is a bond, -CO-, or -SO₂-;

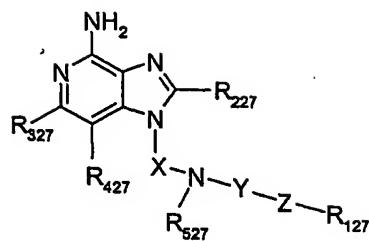
v is 0 to 4; and

each R₂₆ present is independently chosen from C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen, and trifluoromethyl;

and pharmaceutically acceptable salts of any of the foregoing.

30

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines compounds defined by Formula XXVII



wherein

X is alkylene or alkenylene;

Y is --CO-- , --CS-- , or $\text{--SO}_2\text{--}$;

Z is a bond, --O-- , --S-- , or $\text{--NR}_{527}\text{--}$;

R₁₂₇ is aryl, heteroaryl, heterocyclyl, C₁₋₂₀ alkyl or C₂₋₂₀ alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently chosen from:

- 10 -alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- 15 -substituted cycloalkyl;
- O-alkyl;
- O-(alkyl)₀₋₁-aryl;
- O-(alkyl)₀₋₁-heteroaryl;
- O-(alkyl)₀₋₁-heterocyclyl;
- 20 -COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)₀₋₂-alkyl;
- S(O)₀₋₂-(alkyl)₀₋₁-aryl;
- 25 -S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
- S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
- (alkyl)₀₋₁-N(R₅₂₇)₂;
- (alkyl)₀₋₁-NR₅₂₇-CO-O-alkyl;

-(alkyl)₀₋₁-NR₅₂₇-CO-alkyl;
-(alkyl)₀₋₁-NR₅₂₇-CO-aryl;
-(alkyl)₀₋₁-NR₅₂₇-CO-heteroaryl;
-N₃;
5 -halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkyl;
-CO-haloalkoxy;
10 -NO₂;
-CN;
-OH;
-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R₂₂₇ is chosen from:

15 -hydrogen;
-alkyl;
-alkenyl;
-alkyl-O-alkyl;
-alkyl-S-alkyl;
20 -alkyl-O-aryl;
-alkyl-S-aryl;
-alkyl-O- alkenyl;
-alkyl-S- alkenyl; and
-alkyl or alkenyl substituted by one or more substituents chosen
25 from:
-OH;
-halogen;
-N(R₅₂₇)₂;
-CO-N(R₅₂₇)₂;
30 -CS-N(R₅₂₇)₂;
-SO₂-N(R₅₂₇)₂;
-NR₅₂₇-CO-C₁₋₁₀ alkyl;

5 -NR₅₂₇-CS-C₁₋₁₀ alkyl;
 -NR₅₂₇-SO₂-C₁₋₁₀ alkyl;
 -CO-C₁₋₁₀ alkyl;
 -CO-O-C₁₋₁₀ alkyl;
 -N₃;
 -aryl;
 -heteroaryl;
 -heterocyclyl;
 -CO-aryl; and
 -CO-heteroaryl;

10 R₃₂₇ and R₄₂₇ are independently chosen from hydrogen, alkyl, alkenyl,
 halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;
 each R₅₂₇ is independently H or C₁₋₁₀alkyl;
and pharmaceutically acceptable salts thereof.

15 As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of
 both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and
 cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms,
 with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total
 of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably
20 have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl,
 cyclopropylmethyl, cyclopentyl, cyclohexyl and adamantlyl.

25 The term "haloalkyl" is inclusive of groups that are substituted by one or more
 halogen atoms, including perfluorinated groups. This is also true of groups that include
 the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl,
 trifluoromethyl, and the like.

30 The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems.
 Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The
 term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring
 hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl,
 quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl,
 pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl,

pyrimidinyl, benzimidazolyl, quinoxalanyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, and the like.

In some embodiments, the topical formulations of the present invention are prepared using the free base form of the IRM compound.

The amount of an IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to these compounds, and routine testing. The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, or reduction or resolution of actinic keratosis or pre-actinic keratosis lesions.

In general, the amount of the IRM compound present in a topical formulation of the invention will be an amount effective to treat a targeted condition, to prevent recurrence of the condition, or to promote immunity against the condition. The amount or concentration of the IRM compound can range from 0.001% to 10% by weight based on the total formulation weight, such as, for example, from 0.03% to 5.0% by weight, or from 0.1 to 1.0% by weight. In certain embodiments, the amount of the IRM compound is at least 0.003% by weight, such as, for example, at least 0.005%, at least 0.01%, at least 0.03%, at least 0.10%, at least 0.30% and at least 1.0%. In other embodiments, the amount of the IRM compound is at most 5.0% by weight, such as, for example, at most 3.0%, and at most 1.0%.

The topical formulations of the invention additionally comprise a fatty acid. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated,

comprising 6 to 28 carbon atoms, such as, for example, from 10 to 22 carbon atoms. Non-limiting examples of such fatty acids include isostearic acid, oleic acid, and linear- or branched chained carboxylic acids of 6 to 18 carbon atoms. The fatty acid may be present in the formulation in an amount sufficient to solubilize the IRM compound. In one embodiment, the amount of the fatty acid can range from 0.05 % to 40 % by weight based on the total weight of the formulation, such as, for example, from 1% to 30%, from 3% to 15% and from 5% to 10%. In certain embodiments, the amount of the fatty acid is at least 3.0% by weight, such as, for example, at least 5.0%, at least 10.0%, and at least 25%. The fatty acid component of the formulation can comprise one or more fatty acids.

The topical formulations of the invention additionally comprise at least one hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms. By "hydrophobic" is meant that the component is essentially insoluble in water, i.e. immiscible with water and unable to form a micelle in water, and does not contain polyoxyethylene or acid salt groups. Preferably the hydrophobic, aprotic component has a hydrophilic lipophilic balance (HLB) of less than 2. The HLB of a component may be determined as described, for example, in Attwood, D., Florence, A. T. Surfactant Systems: Their Chemistry, Pharmacy, and Biology. New York: Chapman & Hall, 471-473, 1983. By "aprotic" is meant that the component cannot donate a proton to the IRM and does not contain groups such as carboxyl, hydroxy, primary and secondary amino, primary and secondary amido, or quaternary ammonium groups. Preferably this component has a pKa of at least 14.2 and does not substantially solubilize or form a complex such as an acid-base pair or complex or a hydrogen bond complex with the IRM compound. By "not substantially" is meant that the ratio of the IRM compound's solubility in the hydrophilic, aprotic component to that in isostearic acid is less than 1:40.

Formulations intended for dermal or topical use desirably have a certain minimum amount of an oil phase to provide qualities such as spreadability, feel on the skin, texture, and so on. However, if all the components of the oil phase solubilize the IRM, then the degree of saturation of the IRM in the formulation will decrease, making it more difficult to deliver the IRM from the formulation to the skin. Addition of the hydrophobic, aprotic component can increase the oil phase volume of the topical formulation to provide desirable qualities such as spreadability and feel, while at the same time not appreciably altering the degree of saturation or thermodynamic activity of the IRM. For example, the

amount of fatty acid, which solubilizes the IRM, can be reduced to increase the degree of IRM saturation while maintaining a sufficient oil phase volume by virtue of the addition of the hydrophobic, aprotic component, which does not offset the increased IRM saturation. Thus, the topical formulation of the present invention can facilitate both physical property and drug delivery requirements. Degree of saturation and thermodynamic activity of the IRM in these formulations is equal to the IRM concentration in the oil phase divided by the saturation concentration of the IRM in the oil phase. When the topical formulations of the present invention contain saturated IRM the thermodynamic activity or degree of saturation is unity, and when partially saturated the thermodynamic activity or degree of saturation is less than unity.

The amount of the hydrophobic, aprotic component present in a formulation of the invention can range from 1% to 30% by weight based on the total formulation weight, for example, from 3 % to 15% by weight, and from 5 to 10% by weight. In certain embodiments, the amount of the hydrophobic, aprotic component is at least 3.0% by weight, for example, at least 5.0%, and at least 10.0%. The weight ratio of the hydrophobic, aprotic component to the fatty acid can be 0.025:1 to 600:1, for example, 0.5:1 to 50:1, and 2:1 to 30:1. The combined amount (weight percent of the total topical formulation weight) of the hydrophobic, aprotic component and the fatty acid can be 2% to 50% by weight, for example 2% to 30%, 5% to 30%, 5% to 20%, and 10% to 20%.

Examples of useful hydrophobic, aprotic components include but are not limited to fatty acid esters, for example, isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate; triglycerides, for example, caprylic/capric triglyceride; cetyl esters wax; hydrocarbons of 8 or more carbon atoms, for example, light mineral oil, white petrolatum; and waxes, for example, beeswax. In some embodiments, the hydrophobic, aprotic component is chosen from one or more of isopropyl myristate, isopropyl palmitate, caprylic/capric triglyceride, and diisopropyl dimer dilinoleate.

The formulations of the present invention can also comprise a hydrophilic viscosity enhancing agent. Examples of suitable hydrophilic viscosity enhancing agents include cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the

United States Pharmacopoeia. Suitable carbomers include, for example, those available as Carbopol™ 934P, Carbopol 971P, Carbopol 940, Carbopol 974P, Carbopol 980, and Pemulen™ TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio. In one embodiment of the present invention, the viscosity enhancing agent is chosen from Carbopol 974P and 980. When included, the viscosity enhancing agent is generally present in an amount ranging from 0.1% to 10% by weight of total formulation weight, such as, for example, from 0.5 % to 5% by weight, from 0.5% to 1.5% by weight, and from 0.7% to 3% by weight. In certain embodiments, the amount of the viscosity enhancing agent is at least 0.5% by weight, for example, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, and at least 1.0% by weight.

The formulations of the invention can additionally comprise an emulsifier.

Suitable emulsifiers include non-ionic surfactants such as, for example, polysorbate 60, sorbitan monostearate, polyglyceryl-4 oleate, polyoxyethylene(4) lauryl ether, etc. In certain embodiments, the emulsifier is chosen from poloxamers (e.g., Pluronic™ F68, also known as Poloxamer 188, a poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), available from BASF, Ludwigshafen, Germany) and sorbitan trioleate (e.g., Span 85 available from Uniqema, New Castle, DE). If included, the emulsifier is generally present in an amount of 0.1% to 10% by weight of total formulation weight, for example, from 0.5% to 5% by weight, and from 0.75% to 3.5% by weight. In certain embodiments, the amount of the emulsifier is at least 1.0% by weight, for example, at least 2.5%, at least 3.5%, and at least 5.0%.

In certain embodiments of the present invention, the formulation can also include at least one chelating agent. The chelating agent functions to chelate metal ions that may be present in the formulation. Suitable chelating agents include salts of ethylenediaminetetraacetate (EDTA), such as the disodium salt. If included, the chelating agent is generally present in an amount ranging from 0.001 % to 0.1% by weight, and preferably from 0.01% to 0.05% by weight. In certain embodiments, the amount of the chelating agent is at least 0.005% by weight, such as, for example, at least 0.01%, and at least 0.05%.

The formulation can also include a preservative system. The preservative system is generally comprised of at least one preservative compound chosen from methylparaben, ethylparaben, propylparaben, phenoxyethanol, iodopropynyl butylcarbamate, sorbic acid,

a fatty acid monoester of glycerin such as glycerol monolaurate, and a fatty acid monoester of propylene glycol such as propylene glycol monocaprylate. The preservative system may also include a preservative enhancing solubilizer which enhances the solubility of the preservative in the aqueous phase, examples of which include diethylene glycol monoethyl ether and propylene glycol. In one embodiment, the preservative system can be comprised of methylparaben, propylparaben, and propylene glycol. In another embodiment, the preservative system can be comprised of methylparaben, ethylparaben, and diethylene glycol monoethyl ether. In one embodiment, the preservative system can be comprised of phenoxyethanol, methylparaben or methyl- and ethylparaben, and diethylene glycol monoethyl ether. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, diethylene glycol monoethyl ether, and poly(ethylene glycol)(4) monolaurate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol, and diethylene glycol monoethyl ether. In the above embodiments, the methylparaben, ethylparaben, and propylparaben can each be present in the formulations in an amount ranging from 0.01% to 0.5% by weight of the formulation weight, for example, from 0.05 % to 0.25% by weight, and from 0.1% to 0.2% by weight. The iodopropynyl butylcarbamate can be present in the formulations in an amount ranging from 0.01% to 0.1%. The phenoxyethanol can be present in the formulations in an amount ranging from 0.1% to 1%. The propylene glycol and diethylene glycol monoethyl ether can each be present in the formulations in an amount ranging from 1% to 30% by weight of the formulation weight, such as, for example, from 5 % to 25% by weight, and from 10% to 15% by weight. The preservative system can be present in the formulations in an amount ranging from 0.01% to 30% by weight of the formulation weight, for example, from 0.05% to 30%, from 0.1% to 25% by weight, and from 0.2% to 15% by weight. In a further embodiment, the methylparaben, ethylparaben, propylparaben, iodopropynyl butylcarbamate, and phenoxyethanol can be solubilized in propylene glycol, poly(ethylene glycol)(4) monolaurate, or diethylene glycol monoethyl ether prior to addition to the formulation. The preservative system can be selected such that it meets the criteria for antimicrobial effectiveness set forth in the United States Pharmacopeia <51>.

The formulations of the present invention may additionally comprise at least one pH adjuster. Suitable pH adjusters include organic bases and inorganic bases such as, for example, KOH, NaOH. The pH of the topical formulations of the present invention generally ranges from 3.5 to 7.0. In one embodiment, the pH of the topical formulations of the present invention can range from 4.0 to 6.0, preferably 5.0. In another embodiment of the invention, the pH of the topical formulations of the present invention can range from 5.5 to 6.5, preferably 6.0.

Any of the foregoing formulations can be in the form of an oil-in-water emulsion such as a cream or a lotion. Such an emulsion can comprise an oil phase comprising the IRM compounds, a fatty acid in an amount sufficient to solubilize the IRM compounds, a hydrophobic, aprotic component; and an aqueous phase comprising a hydrophilic viscosity enhancing agent, for example, a carbomer. In certain embodiments, the amount or concentration of the IRM in the oil phase can be at least 0.01%, for example, at least 0.02%, at least 0.1%, and at least 1% with respect to oil phase weight. In other 15 embodiments, the amount or concentration of the IRM in the oil phase can be at most 20%, for example, at most 10%, and at most 5% with respect to oil phase weight. The emulsion can be preserved so that when challenged by an antimicrobial effectiveness test, it meets regulatory requirements for topical creams packaged in multiple-use containers.

Any of the foregoing formulations according to the present invention can 20 be applied to the dermal surfaces of a mammal. Depending on the IRM compound concentration, formulation composition, and dermal surface, the therapeutic effect of the IRM compound may extend only to the superficial layers of the dermal surface or to tissues below the dermal surface. Thus, another aspect of the present invention is directed to a method for the treatment of a dermal associated condition comprising applying to skin 25 one of the foregoing formulations. As used herein, a "dermal associated condition" means an inflammatory, infectious, neoplastic or other condition that involves a dermal surface or that is in sufficient proximity to a dermal surface to be affected by a therapeutic agent topically applied to the dermal surface. Examples of a dermal associated condition include warts, atopic dermatitis, basal cell carcinoma, postsurgical scars, and actinic 30 keratosis.

In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratoses are premalignant lesions considered

biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.

5 In some embodiments, the above described formulations are particularly advantageous for dermal application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM.

10

EXAMPLES

The following Examples are provided to further describe various IRM formulations and methods according to the invention. The examples, however, are not intended to limit the formulations and methods within the spirit and scope of the invention.

Examples 1-7 and Comparative Example C1

15 Table 1 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 1

Ingredient (Compendial Status)	Topical Cream (percentage weight-by-weight)					
	Comparative Example C1 (Placebo)	Example 1	Example 2	Example 3	Example 4	Example 5
IRM Compound 1	0.00	0.001	0.003	0.010	0.03	0.10
Isostearic Acid	5.00	5.00	5.00	5.00	5.00	7.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	10.00	10.00	8.00
Carbomer 974P (NF)	1.00	1.00	1.00	1.00	1.00	1.00
Polyoxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10
Edetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.50	0.50	0.55
Purified Water (USP)	65.65	65.649	65.647	65.64	65.62	65.55
Total	100.00	100.00	100.00	100.00	100.00	100.00

The formulations set forth in Table 1 were prepared in the following manner:

Oil phase preparation: 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]

[1,5]naphthyridin-4-amine (IRM compound 1) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

5 Water phase preparation: Edeitate disodium was dissolved in the water.

Methylparaben and propylparaben were dissolved in propylene glycol and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

Phase combination: The oil phase was added to the water phase at ambient conditions.

10 The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Formulations containing 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]

15 [1,5]naphthyridin-4-amine (IRM Compound 1) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 1. The formulations described above were tested by examining tissue and serum concentrations of TNF- α , MCP-1
20 (monocyte chemoattractant protein-1) and IFN- α cytokines following drug treatment.

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams were used in all studies. Animals were randomized to treatment groups and dosed five per treatment group.

25 The rats were acclimated to collars around the neck on two consecutive days prior to actual dosing. The rats were collared before dosing to prevent ingestion of the drug, and were then dosed topically with 50 μ L of active cream or the appropriate placebo on right flank and then housed individually following dosing. At various times following dosing, the rats were anesthetized and blood was collected by cardiac puncture. Blood was allowed to clot at room temperature and serum was separated from the clot via centrifugation and stored at -20 °C
30 until it was analyzed for cytokine concentrations.

Following blood collection, the rats were euthanized and their skins removed. Tissue from both treated site (at) and contralateral site (away) were obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial and flash frozen in liquid nitrogen. The frozen tissue sample was then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue was homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 1 minute. The tissue suspension was then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant collected and stored at -20 °C until analyzed for cytokine concentrations.

ELISAs for rat MCP-1 were purchased from BioSource Intl. (Camarillo, CA) and rat TNF- α were purchased from BD Pharmingen (San Diego, CA) and performed according to manufacturer's specifications. Results for both TNF- α , and MCP-1 were expressed in pg/200 mg tissue or pg/ml serum. The sensitivity of the TNF- α ELISA was 31.2 pg/ml and of the MCP-1 ELISA was 11.7 pg/ml. IFN- α concentrations in both serum and skin tissue were determined using a bioassay that measured inhibition of the viral cytopathic effect of vesicular stomatitis virus on rat LMS-C2 fibroblast cells as previously described (Reiter, M. J., Testerman, T. L., Miller, R. L., Weeks, C. E., and Tomai, M. A. (1994) "Cytokine Induction in Mice by the Immunomodulator Imiquimod." *J. Leukocyte Biol.* 55, 234-240). IIT Research Institute, Chicago IL, performed these assays. Results for IFN- α concentrations were normalized to a standard reference rat IFN- α , preparation with results being reported in U/mL and are normalized per mg of tissue.

The data shown below in Tables 2-4 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

In order to determine the kinetics of local and systemic cytokine production following local administration of IRM Compound 1, the full time course study (Study 1 with results in Table 2) was done by topically dosing rats with the topical cream formulation of Example 7.

Serum and tissue samples were taken at 1, 2, 4, 8, 16, 24 and 48 hours post dose. Multiple cytokines (MCP-1, TNF- α and IFN- α) were analyzed separately.

With the tissue data, for each hour measured, a paired t-test (used to eliminate within subject variability) analyzed the difference between treated tissue and control tissue from the same animal. A p-value less than alpha=0.05 indicated a statistically significant difference between the treated and control tissue at that hour. The data are presented in Table 2.

Table 2. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 7 Full Time Course^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		TNF- α		
		Serum	Treated Site	Control site
0	untreated	0	NA	96+5
16	placebo	0	103+8	71+6
1	1%	6+6	318+33 ^c	96+13
2	1%	0	1125+74 ^c	124+18
4	1%	0	1120+51 ^c	129+11
8	1%	24+16	429+56 ^c	91+12
16	1%	6+4	231+22 ^c	87+27
24	1%	32+32	198+28 ^c	103+13
48	1%	49+49	74+10	69+15
		MCP-1		
0	untreated	81+30	NA	44+2
16	placebo	144+9	144+41	42+3
1	1%	86+29	40+8	42+3
2	1%	123+31	234+29 ^c	50+4
4	1%	101+28	723+89 ^c	41+5
8	1%	438+91 ^c	1474+202 ^c	38+3
16	1%	424+96 ^c	1209+325 ^c	31+5
24	1%	187+39	813+151 ^c	39+1
48	1%	141+24	145+48 ^c	36+6
		IFN- α		
0	untreated	<200	NA	<650
16	placebo	<200	<650	<650
1	1%	<200	<650	<650
2	1%	<200	<650	<650
4	1%	<200	<650	<650
8	1%	<200	3/5>650	<650
16	1%	<200	<650	<650
24	1%	<200	<650	<650
48	1%	<200	<650	<650

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^bTNF- α and MCP-1 were measured by ELISA. IFN- α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals \pm SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

5 A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 3). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 5. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1.

10 An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multiple- or single-use) and time point prior to analysis. Again, placebo data were recorded only at the 8-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 3 below.

Table 3. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 5 Multiple vs. Single Dose^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		MCP-1		
		Serum	Treated Site	Control Site
0	None (untreated)	89±11	NA	20±10
24	Placebo	41±14	42±15	28±6
8	Multiple 0.1%	71±13	784±48 ^c	42±5
24	Multiple 0.1%	105±36	145±23 ^c	32±6
8	Single 0.1%	73±9	519±99 ^c	33±6
24	Single 0.1%	82±3 ^c	412±130 ^c	35±7

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^b MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A dose response study (Study 3 with results shown in Table 4) was performed by dosing with the topical cream formulations of Examples 3-5 and 7, containing various concentrations of IRM Compound 1. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 1 for its ability to affect a local MCP-1 induction at four concentrations.

Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 24 hours post dose and these observations were compared to each time point for the active group.

Table 4. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 3-5 and 7^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		MCP-1		
		Serum	Treated Site	Control Site
0	controls	207+96	NA	38+12
24	placebo (Comparative Example C1)	367+178	61+14	20+5
8	0.01% (Example 3)	81+23	61+12	36+7
8	0.03% (Example 4)	81+20	271+29	48+5
8	0.1% (Example 5)	153+14	1119+122 ^c	51+8
8	1.0% (Example 7)	136+23	1370+99 ^c	50+15
24	0.01% (Example 3)	71+18	183+49 ^c	33+13
24	0.03% (Example 4)	71+20	212+49 ^c	40+7
24	0.1% (Example 5)	226+73	628+127 ^c	40+11
24	1.0% (Example 7)	149+45	756+38 ^c	30+9

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^b MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals \pm SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

10

Examples 8-13

Table 5 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 5

Ingredient (Compendial Status)	Topical Cream (percentage weight-by-weight)					Example 13
	Example 8	Example 9	Example 10	Example 11	Example 12	
IRM Compound 2	0.01	0.03	0.10	1.00	0.003	0.30
Isostearic Acid	5.00	5.00	5.00	10.00	5.00	5.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	5.00	10.00	10.00
Carbomer 974P (NF)	1.00	1.00	1.00	0.75	1.00	1.00
Poloxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10
Eddetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.35	0.50	0.50
Purified Water (USP)	65.64	65.62	65.55	65.05	65.647	65.35
Total	100.00	100.00	100.00	100.00	100.00	100.00

The formulations set forth in Table 5 were prepared in the following manner:

5 Oil phase preparation: N-[4-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*] [1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

10 Water phase preparation: Edeate disodium was dissolved in the water. Methylparaben and propylparaben were dissolved in propylene glycol, and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

15 Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured, and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

20 Formulations containing N-[4-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*] [1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 2. The formulations described above were tested by examining tissue and serum concentrations of TNF- α , MCP-1 and IFN- α following drug treatment as described in Examples 1-7.

25 The data shown below in Tables 6-8 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

In order to determine the kinetics of local and systemic cytokine production following local administration of IRM Compound 2, the full time course study (Study 1 with results in Table 6) was done by topically dosing rats with the topical cream formulation of Example 11 as described in Examples 1-7. The data are presented in Table 6.

Table 6. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 11 Full Time Course^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		TNF- α		
		Serum	Treated Site	Control site
0	untreated	29+15	NA	70+11
16	placebo	42+9	131+32	69+11
1	1%	38+38	44+14	35+19
2	1%	2+2	75+20 ^c	33+13
4	1%	3+3	321+18 ^c	62+20
8	1%	0	894+180 ^c	21+9
16	1%	12+12	377+45 ^c	22+12
24	1%	16+8	285+15 ^c	52+14
48	1%	24+7	74+9	65+13
		MCP-1		
0	untreated	100+20	NA	33+7
16	placebo	144+9	225+106	22+4
1	1%	117+17	56+9	55+9
2	1%	126+29	50+13	54+8
4	1%	136+29	161+18 ^c	71+9
8	1%	189+28	1020+319	45+15
16	1%	297+35	1294+122 ^c	40+9
24	1%	217+12	1044+185 ^c	41+11
48	1%	120+22	134+14 ^c	34+7
		IFN- α		
0	untreated	<65	NA	<650
16	placebo	<65	<650	<650
1	1%	<65	<650	<650
2	1%	<65	<650	<650
4	1%	<65	<650	<650
8	1%	<65	901+571	<650
16	1%	<65	1330+386 ^c	<650
24	1%	<65	<650	<650
48	1%	<65	<650	<650

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^bTNF- α and MCP-1 were measured by ELISA. IFN- α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals \pm SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

5 A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 7). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 10. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1.

10 An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multi or single use) and time point prior to analysis. Again, placebo data were recorded only at the 16-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 7 below.

Table 7. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 10 Multiple vs. Single Dose^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		MCP-1		
		Serum	Treated Site	Control Site
0	None (untreated)	161±58	NA	80±22
16	Placebo	214±35	71±16	47±11
16	Multiple 0.1%	321±62	1173±117 ^c	86±14
24	Multiple 0.1%	217±43	388±80 ^c	58±5
16	Single 0.1%	205±32	1448±241 ^c	77±15
24	Single 0.1%	279±45	1172±288 ^c	90±15

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^b MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A dose response study (Study 3 with results shown in Table 8) was performed by dosing with the topical cream formulations of Examples 8-11, containing various concentrations of IRM Compound 2. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 2 for its ability to affect a local MCP-1 induction at four concentrations.

Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 16 hours post dose and these observations were compared to each time point for the active group.

Table 8. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 8-11^a

Time (hours) Post Dose	Dose	Cytokine Concentration ^b		
		MCP-1		
		Serum	Treated Site	Control Site
0	controls	293±23	NA	41±11
16	placebo (Comparative Example C1)	293±76	44±10	36±12
16	0.01% (Example 8)	276±50	257±85	57±20
16	0.03% (Example 9)	318±86	210±10	45±9
16	0.10% (Example 10)	529±141	2622±616 ^c	73±9
16	1.0% (Example 11)	345±51	3166±470 ^c	71±11
24	0.01% (Example 8)	298±65	276±87	94±32
24	0.03% (Example 9)	253±34	427±238	28±14
24	0.10% (Example 10)	331±93	1461±264 ^c	19±7
24	1.0% (Example 11)	358±52	1952±185 ^c	17±6

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^b MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

^cIndicates p<0.05 when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

5

Examples 14 – 18

Table 9 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 9

Ingredients	Topical Creams (percentage weight-by-weight)				
	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
IRM Compound 1	0.01	0.10	1.00	3.00	1.00
Isostearic Acid (874)	5.00	5.00	10.00	25.00	10.00
*Diisopropyl dimer dilinoleate	10.00	10.00	5.00	5.00	-
**Caprylic/capric triglycerides	-	-	-	-	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.90	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50
Purified Water	70.94	70.85	69.95	52.55	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.60	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00

*Available under the trade name PRIPURE 3786 from Uniquema, New Castle, DE

**Available under the trade name Crodamol GTCC-PN from Croda, Inc, Parsippany, NJ

5

Examples 19 – 24

Table 10 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 10

Ingredients	Topical Creams (percentage weight-by-weight)					
	Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24
IRM Compound 2	0.003	0.03	0.10	1.00	3.00	1.00
Isostearic Acid (874)	5.00	5.00	5.00	10.00	25.00	10.00
Diisopropyl dimer dilinoleate	10.00	10.00	10.00	5.00	5.00	-
Caprylic/capric triglycerides	-	-	-	-	-	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.70	0.60	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50	2.50
Purified Water	70.95	70.92	70.85	69.95	53.19	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.40	0.26	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00	100.00

The formulations described in Tables 9 and 10 were prepared using the following general method:

5

Oil phase preparation:

The IRM compound was dissolved in isostearic acid and diisopropyl dimer dilinoleate (or caprylic/capric acid triglyceride) with heat if necessary.

Water phase preparation:

Edetate disodium was dissolved in the water. Poloxamer 188 was then added to the water phase and mixed until dissolved. Carbomer 980 was then added to the water phase and mixed until the carbomer was fully dispersed and hydrated. Methylparaben and propylparaben were dissolved in diethylene glycol monoethyl ether and the solution was subsequently added to the water phase.

Phase combination:

The water phase was added to the oil phase at ambient conditions. The emulsion was then mixed at high speed or homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Examples 25 – 28

Table 11 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 11

Ingredient	Topical Cream (percentage weight-by-weight)			
	Ex. 25	Ex. 26	Ex. 27	Ex. 28
IRM Compound 1	1	1	1	1
Isostearic Acid (874)	10	10	10	8
Diisopropyl dimer dilinoleate	5	5	5	1
Carbomer 980, NF	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether USA - NF	10	10	10	10
Disodium EDTA, USP	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben, NF	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2
20% (w/w) NaOH	0.4	0.4	0.4	0.4
10% iodopropynyl butylcarbamate in PEG-4 laurate	-	1	-	-
Phenoxyethanol	-	-	0.5	-

Examples 29 – 135

5 Topical creams containing the IRM compounds listed in Table 12 were prepared using the general methods described above for Examples 1 – 24. Each IRM was formulated into one or more of the model formulations shown in Tables 13 and 14. Table 15 summarizes the topical creams that were prepared.

Table 12

IRM Compound	Chemical Name
3	1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
4	1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,8]naphthyridin-4-amine
5	2-butyl-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,8]naphthyridin-4-amine
6	1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine
7	2-methylthiazolo[4,5- <i>c</i>]quinolin-4-amine
8	2-ethoxymethyl-1-phenylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine
9	2-ethylthiazolo[4,5- <i>c</i>]quinolin-4-amine
10	4-amino-2-butyl- α,α -dimethyl-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridine-1-ethanol
11	N ¹ -[2-(4-amino-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)ethyl]benzamide
12	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
13	1-(2-phenoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
14	1-[(R)-1-phenylethyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine
15	N ⁴ -[4-(4-amino-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)butyl]-4-morpholinecarboxamide
16	N ³ -[4-(4-amino-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)butyl]nicotinamide
17	1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
18	1-[2-(pyridin-4-ylmethoxy)ethyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
19	2-methyl-1-[5-(methylsulfonyl)pentyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
20	N-[3-(4-amino-2-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)propyl]cyclohexanecarboxamide
21	N-[3-(4-amino-2-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)propyl]-2-methylpropanamide
22	N-[3-(4-amino-2-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)propyl]butanamide

IRM Compound	Chemical Name
23	2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
24	N-{2-[4-amino-2-(ethoxymethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl]ethyl}ethanesulfonamide
25	N-{2-[4-amino-2-(ethoxymethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl]ethyl}propanamide
26	1-[2-(methylsulfonyl)ethyl]-2-propyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
27	N-{2-[4-amino-2-(ethoxymethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl]ethyl}-N'-ethylthiourea
28	2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
29	2-ethyl-1-[4-(ethylsulfonyl)butyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
30	N-{3-[4-amino-2-(ethoxymethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl]propyl}cyclopentanecarboxamide
31	N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]pyridin-1-yl]propyl}morpholine-4-carboxamide
32	1-(2-methylpropyl)-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
33	8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5- <i>c</i>]quinolin-6-amine
34	4-amino- $\alpha,\alpha,2$ -trimethyl-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinoline-1-ethanol
35	2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine
36	2-butyl-1-(2-phenoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine
37	N-[3-(4-amino-2-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)propyl]methanesulfonamide

Table 13

Ingredient	Model Formulation (percentage weight-by-weight)						
	A	B	C	D	E	F	G
IRM	0.01	0.1	1	1	1	1	1
Isostearic acid	5	5	5	20	42	13	6
Isopropyl myristate	10	10	10	10	2	10	10
Carbomer 974P	1	1	1	1	1	1.5	1
Purified water	*	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	15	15	15	15	13	15	15
Xanthan gum	-	-	-	-	0.4	-	-
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.7	0.7	0.7	0.7	0.7	0.7	0.7

*Qs to 100

Table 14

Ingredient	Model Formulation (percentage weight-by-weight)					
	H	I	J	K	L	M
IRM	0.01	0.1	1	1	3	5
Isostearic acid	5	5	5	10	10	10
Diisopropyl dimer dilinoleate	10	10	10	5	5	5
Carbomer 980	0.7	0.7	0.7	1.0	1.0	1.0
Purified water	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.6	2.6	2.6
Diethylene glycol monoethyl ether	10	10	10	10	10	10
Xanthan gum	-	-	-	0.1	0.1	0.1
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.4	0.4	0.4	0.4	0.4	0.4

*Qs to 100

Table 15

Example	IRM Compound	Model Formulation
29	3	A
30	3	B
31	3	C
32	4	A
33	4	B
34	4	C
35	5	A

Example	IRM Compound	Model Formulation
36	5	B
37	5	D
38	6	A
39	6	B
40	6	C
41	7	A
42	7	B
43	7	C
44	8	A
45	8	B
46	8	C
47	9	A
48	9	B
49	9	C
50	10	A
51	10	B
52	10	C
53	11	A
54	11	B
55	11	E
56	12	A
57	12	B
58	12	C
59	13	A
60	13	B
61	13	F
62	14	A
63	14	B

Example	IRM Compound	Model Formulation
64	14	G
65	15	H
66	15	I
67	15	K
68	16	H
69	16	I
70	16	K
71	17	A
72	17	B
73	17	C
74	18	H
75	18	I
76	18	K
77	19	H
78	19	I
79	19	K
80	20	H
81	20	I
82	20	K
83	20	L
84	20	M
85	21	H
86	21	I
87	21	K
88	22	H
89	22	I
90	22	J
91	23	H

Example	IRM Compound	Model Formulation
92	23	I
93	23	J
94	24	H
95	24	I
96	24	K
97	25	H
98	25	I
99	25	K
100	26	H
101	26	I
102	26	K
103	27	H
104	27	I
105	27	K
106	28	H
107	28	I
108	28	K
109	29	H
110	29	I
111	29	K
112	30	H
113	30	I
114	30	K
115	31	H
116	31	I
117	31	K
118	32	A
119	32	B

Example	IRM Compound	Model Formulation
120	32	C
121	33	A
122	33	B
123	33	C
124	34	A
125	34	B
126	34	C
127	35	A
128	35	B
129	35	C
130	36	A
131	36	B
132	36	C
133	37	H
134	37	I
135	37	K

The topical creams of Examples 29 –135 were tested using the test method described below. The results are shown in Table 16 below where each value is the mean of the values from the 3 rats in the treatment group.

5

10

SINGLE DOSE MCP-1 INDUCTION TEST METHOD

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 µL dose of active cream or the appropriate placebo is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed

individually to prevent ingestion of the drug. At selected post treatment time points, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature. Serum is separated from the clot via centrifugation, and stored at -20°C until it is analyzed for MCP-1 concentration.

5 Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant is collected and stored at -20°C until 10 analyzed for MCP-1 concentration.

15

ELISAs for rat MCP-1 are purchased from BioSource Intl. (Camarillo, CA) and performed according to manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml.

Table 16

Cream of Example	MCP-1 (pg/ml)						Placebo Cream	
	RM Cream			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated		
29	123	202	46	291	55	34	142	
30	119	92	31	177	201	43	142	
31	212	1235	54	267	606	125	142	
32	26	54	59	79	82	69	54	
33	54	70	71	56	74	58	54	
34	72	88	58	59	319	69	54	
35	170	110	55	162	142	62	80	
36	94	674	46	86	1216	96	80	
37	153	1826	38	136	2036	77	80	
38	178	65	120	211	121	86	142	
							59	

Cream of Example	MCP-1 (pg/ml)						Placebo Cream	
	RM Cream			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated		
39	193	220	61	259	263	59	142	
40	226	1204	58	284	1086	95	142	
41	54	82	96	45	88	71	73	
42	65	129	78	54	126	88	73	
43	77	824	68	89	1016	93	73	
44	86	256	*	177	488	*	128	
45	172	1444	*	157	1041	*	128	
46	177	1720	*	406	1023	*	128	
47	58	53	59	81	95	73	37	
48	71	200	61	63	112	61	37	
49	92	1254	62	83	1436	75	37	
50	170	1033	56	*	655	56	88	
						*		

Cream of Example	MCP-1 (pg/ml)							
	IRM Cream				Placebo Cream			
	6 hours		24 hours		6 hours		24 hours	
Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated	Serum
51	625	551	787	*	149	787	88	*
52	811	348	314	*	86	314	88	*
53	70	63	46	76	47	45	7	31
54	68	35	27	71	26	24	7	31
55	75	35	21	44	33	32	7	31
56	115	44	*	115	425	*	201	**42
57	119	411	*	267	1252	*	201	**42
58	190	1560	*	476	1508	*	201	**42
59	155	46	36	271	41	53	107	54
60	123	53	58	175	80	69	107	54
61	133	172	52	151	1131	46	107	54
62	143	211	55	174	428	61	96	26

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	Serum	Treated	Untreated	Serum	Treated	Untreated
63	320	1614	51	230	1217	74
64	970	1094	529	425	390	99
65	43	34	57	46	81	61
66	29	73	28	32	42	74
67	19	54	61	25	34	72
68	60	77	82	91	72	35
69	143	74	52	99	73	59
70	59	77	34	91	134	60
71	259	79	62	134	84	57
72	138	255	65	122	990	63
73	251	999	63	293	1411	108
74	99	66	71	73	99	89
						61
						91

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	Serum	Treated	Untreated	Serum	Treated	Untreated
75	76	101	78	3	170	73
76	66	6779	64	188	4949	104
77	28	47	35	21	43	40
78	27	35	37	33	49	59
79	24	41	40	27	50	38
80	51	59	23	50	163	0
81	9	0	15	83	34	10
82***	61	32	0	121	303	45
82***	50	149	36	79	225	76
83	110	164	124	61	275	172
84	59	177	92	98	629	40
85	81	0	0	0	0	177
						0

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	Serum	Treated	Untreated	Serum	Treated	Untreated
86	116	0	0	0	0	0
87	69	0	0	0	0	177
88	114	56	41	87	43	42
89	74	47	49	132	49	40
90	91	96	47	111	109	41
91	42	91	53	86	874	57
92	83	1238	74	92	1087	67
93	98	2037	64	114	1124	74
94	102	98	107	48	136	133
95	49	130	90	95	158	112
96	68	255	79	132	528	81
97	34	88	106	54	95	92
					36	102

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	Serum	Treated	Untreated	Serum	Treated	Untreated
98	17	116	108	83	123	91
99	51	150	89	43	945	76
100	111	81	83	55	115	72
101	33	72	55	75	209	64
102	79	489	54	112	3199	103
103	82	88	69	31	107	94
104	13	66	55	61	72	63
105	75	83	87	54	60	69
106	72	96	103	64	168	158
107	21	129	98	48	168	75
108	95	314	72	135	3267	128
109	72	60	71	71	78	62

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	6 hours		24 hours			
Serum	Treated	Untreated	Serum	Treated	Untreated	Serum
110	44	76	57	92	72	75
111	70	143	83	32	2397	68
112	66	67	120	28	84	70
113	46	107	106	70	1034	93
114	14	627	65	196	2880	111
115	39	38	41	84	77	90
116	73	81	90	64	57	223
117	66	113	52	79	91	61
118	132	59	59	135	46	52
119	123	184	31	144	104	42
120	124	1261	45	171	892	56
121	90	74	51	88	96	75

Cream of Example	MCP-1 (pg/ml)					
	IRM Cream			Placebo Cream		
	Serum	Treated	Untreated	Serum	Treated	Untreated
122	72	415	50	91	613	82
123	156	1502	52	226	1043	48
124	92	94	27	96	95	110
125	123	198	128	107	72	120
126	136	1828	97	73	1348	349
127	67	66	46	81	90	22
128	63	80	58	55	53	35
129	49	382	58	35	809	59
130	132	55	41	135	162	43
131	124	279	59	144	822	60
132	124	1901	13	171	1212	11
133	64	106	0	52	199	32
						26
						8

Cream of Example	MCP-1 (pg/ml)							
	IRM Cream			Placebo Cream				
	6 hours		24 hours					
Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated	
134	9	76	0	70	59	0	26	8
135	59	89	0	76	47	0	26	8

*MCP-1 concentration was not measured

**MCP-1 concentration is for the treated site.

***The cream of Example 82 was used in 2 separate experiments

Examples 136 – 140

Table 17 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

5

Table 17

Ingredients	Topical Creams (percentage weight-by-weight)				
	Ex. 136	Ex. 137	Ex. 138	Ex. 139	Ex. 140
IRM Compound 1	1	1	1	1	1
Isostearic Acid	10	10	8	10	10
Diisopropyl dimer dilinoleate	-	5	1	5	5
Caprylic/capric triglycerides	5	-	-	-	-
Carbomer 980	0.7	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether	10	10	10	10	10
Disodium EDTA	0.05	0.05	0.05	0.05	0.05
Poloxamer 188	2.5	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben	0.2	0.1	0.2	0.2	0.2
Ethylparaben	0.2	0.1	0.2	0.2	0.2
20% (w/w) NaOH	Qs to pH 5 – 5.5	Qs to pH 5 – 5.5	Qs to pH 5 – 5.5	Qs to pH 6.5	Qs to pH 5 – 5.5
Iodopropynyl butylcarbamate	-	0.1	-	-	-
PEG-4 Laurate	-	0.9	-	-	-
Phenoxyethanol	-	1	-	-	-
Sorbic acid	-	0.15	-	-	-

The topical creams of Examples 136 –140 were tested using the test method described below. The results are shown in Table 18 below where each value is the mean of the values from the 3 rats in the treatment group. “Normal animals” did not receive any treatment.

5

SINGLE DOSE CYTOKINE INDUCTION TEST METHOD

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

10 The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 µL dose of active cream is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed individually to prevent ingestion of the drug. At 6 hours post treatment, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature, serum is separated from 15 the clot via centrifugation, and stored at
–20°C until it is analyzed for cytokine concentrations.

20 Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 25 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris. The supernatant is collected and stored at –20°C until analyzed for cytokine concentrations.

ELISAs for rat MCP-1 are purchased from BioSource Intl. (Camarillo, CA) and rat TNF- α are purchased from BD Pharmingen (San Diego, CA) and performed according to

manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml and the sensitivity of the TNF- α ELISA is 31 pg/ml.

Table 18

Cream of Example	IRM Cream Treated Animals						Cytokine Induction						Normal Animals					
	MCP-1 (pg/ml)			TNF- α (pg/ml)			MCP-1 (pg/ml)			TNF- α (pg/ml)			MCP-1 (pg/ml)			TNF- α (pg/ml)		
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue
136	119	1208	51	64	808	85	73	39	64	67								
137	90	1815	78	78	597	78	73	39	64	67								
138	5	1351	27	66	636	69	73	39	64	67								
139	62	1509	85	50	443	75	73	39	64	67								
140	24	2373	28	80	948	95	73	39	64	67								

What is Claimed is:

1. A pharmaceutical formulation comprising:

an immune response modifier (IRM) compound selected from imidazoquinoline amines,

imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused

5 cycloalkylimidazopyridine amines, 1,2- bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

a fatty acid;

10 a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

2. The formulation according to claim 1 wherein the formulation further

15 comprises a preservative system and an emulsifier.

3. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

20 4. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a pKa greater than 14.2.

5. The formulation according to claim 1 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

25

6.. The formulation according to claim 1 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

7. The formulation according to claim 1 wherein the fatty acid is isostearic acid.

8. The formulation according to claim 1 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.
- 5 9. The formulation according to claim 8 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or a combination thereof.
- 10 10. The formulation according to claim 8 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.
- 15 11. The formulation according to claim 1 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.
- 20 12. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.
- 25 13. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.
14. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate.
- 30 15. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.
16. The formulation according to claim 2 wherein the preservative system

comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

17. The formulation according to claim 2 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

5

18. The formulation according to claim 2 wherein the preservative system comprises a preservative enhancing solubilizer.

10 19. The formulation according to claim 18 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

20. The formulation of claim 2 comprising:

(a) 0.001 to 5% w/w

15 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
20 2-methylthiazolo[4,5-*c*]quinolin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
2-ethylthiazolo[4,5-*c*]quinolin-4-amine,
4-amino-2-butyl- α,α -dimethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine-1-ethanol,
1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
25 1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
1-[(R)-1-phenylethyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
1-[2-(pyridin-4-ylmethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine,

N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]cyclohexanecarboxamide,
2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}
5 ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}propanamide,
1-[2-(methylsulfonyl)ethyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
10 2-ethyl-1-[4-(ethylsulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}cyclopentanecarboxamide,
1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine,
15 4-amino- $\alpha,\alpha,2$ -trimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-
1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
or a combination thereof;
20 (b) 0.05 to 40% w/w isostearic acid;
(c) 1 to 30% w/w hydrophobic, aprotic component;
(d) 0.5 to 10% w/w emulsifier;
(e) 0.01 to 30% w/w preservative system; and
(f) 0.1 to 10% carbomer.

25

21. The formulation of claim 20 comprising:

(a) 0.03 to 3% w/w 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine, or a combination thereof;

- (b) 3 to 25% w/w isostearic acid;
- (c) 3 to 15% w/w hydrophobic, aprotic component;
- (d) 0.75 to 3.5% w/w emulsifier;
- (e) 0.1 to 25% w/w preservative system; and
- 5 (f) 0.5 to 5% w/w carbomer.

22. A method of treating a dermal associated condition, the method comprising a step of: applying to skin a formulation comprising an immune response modifier (IRM) selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carboomers.
- 10
23. The method according to claim 22 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.
- 15
24. The method according to claim 22 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.
- 20
25. The method according to claim 22 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.
26. The method according to claim 25 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.
- 30

27. The method according to claim 22 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.

5 28. The method according to claim 22 wherein the topical formulation further comprises:

a preservative system; and
an emulsifier.

10 29. The method according to claim 22 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
15 1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-methylthiazolo[4,5-c]quinolin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-ethylthiazolo[4,5-c]quinolin-4-amine,
4-amino-2-butyl- α,α -dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
20 1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,
25 N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]
cyclohexanecarboxamide,
2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} propanamide,
5 1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl} cyclopentanecarboxamide,
10 1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,
4-amino- $\alpha,\alpha,2$ -trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-
1H-imidazo[4,5-c]quinolin-4-amine,
15 2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

30. The method according to claim 22 wherein the dermal associated condition is selected from actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.
20

31. The method according to claim 30 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
25 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-methylthiazolo[4,5-c]quinolin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
30 2-ethylthiazolo[4,5-c]quinolin-4-amine,

- 4-amino-2-butyl- α,α -dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
5 1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]
cyclohexanecarboxamide,
2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
10 N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}
ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}
propanamide,
1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,
15 2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl}
cyclopentanecarboxamide,
1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
20 8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,
4-amino- α,α ,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-
1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination
25 thereof.

32. The method according to claim 30 wherein the formulation further comprises a preservative system and an emulsifier.

30 33. The method according to claim 32 wherein the preservative system comprises

methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

34. The method according to claim 32 wherein the preservative system comprises
5 methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

35. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate.

10 36. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

15 37. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

38. The method according to claim 32 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

20 39. The method according to claim 32 wherein the preservative system comprises a preservative enhancing solubilizer.

40. The method according to claim 39 wherein the preservative enhancing
25 solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

41. A method for delivering an immune response modifier (IRM) to a dermal surface, the method comprising the steps of:
30 selecting a formulation comprising:

- (a) an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2- bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;
- 5 (b) a fatty acid;
- (c) a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and
- 10 (d) a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers; and

15 applying the selected topical formulation to the dermal surface.

42. A pharmaceutical formulation comprising:

an immune response modifier (IRM) compound selected from the group consisting of imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines;

20 a fatty acid; and

a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

43. The formulation according to claim 42 wherein the formulation further

25 comprises a preservative system.

44. The formulation according to claim 42 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

30 45. The formulation according to claim 42 wherein the hydrophobic, aprotic

component has a pKa greater than 14.2.

46. The formulation according to claim 42 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

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47. The formulation according to claim 42 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

48. The formulation according to claim 42 wherein the fatty acid is isostearic acid.

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49. The formulation according to claim 42 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

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50. The formulation according to claim 49 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

51. The formulation of claim 49 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.

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52. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

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53. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

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54. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate.

55. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

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56. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

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57. The formulation according to claim 43 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

58. The formulation according to claim 43 wherein the preservative system comprises a preservative enhancing solubilizer.

15

59. The formulation according to claim 58 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

60. The formulation of claim 43 comprising:

20

(a) 0.001 to 5% w/w imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, thiazolonaphthyridine amine, or a combination thereof;

(b) 0.05 to 40% w/w isostearic acid;

(c) 1 to 30% w/w hydrophobic, aprotic component; and

(d) 0.01 to 30% w/w preservative system.

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61. The formulation of claim 43 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

62. The formulation of claim 60 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

5 63. The formulation of claim 62 wherein the viscosity enhancing agent comprises a carbomer.

64. The formulation of claim 63 comprising:

(a) 0.03 to 3% w/w

2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

10 N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

4-amino-2-butyl- α , α -dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

15 1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

or a combination thereof;

(b) 3 to 25% w/w isotearic acid;

(c) 3 to 15% w/w hydrophobic, aprotic component;

20 (d) 0.1 to 25% w/w preservative system;

(e) 0.75 to 3.5% w/w emulsifier; and

(f) 0.5 to 5% w/w carbomer.

65. A method of treating a dermal associated condition, the method comprising a step of:

25 applying to skin a formulation comprising an immune response modifier (IRM) chosen from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

66. The method according to claim 65 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

67. The method according to claim 65 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

5 68. The method according to claim 65 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

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69. The method according to claim 68 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

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70. The method according to claim 65 wherein the formulation further comprises:

a preservative system; and
an emulsifier.

20

71. The method according to claim 65 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine, 1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, 2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, 4-amino-2-butyl- α,α -dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol, 1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, 2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

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72. The method according to claim 65 wherein the dermal associated condition is actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

73. The method according to claim 72 wherein the IRM is 2-methyl-1-(2-methylpropyl)-

5 1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

10 4-amino-2-butyl- α,α -dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

15 74. The method according to claim 72 wherein the formulation further comprises: a preservative system; and an emulsifier.

75. The method according to claim 74 wherein the preservative system comprises

20 methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben

at 0.01 to 0.5% w/w of the formulation.

76. The method according to claim 74 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben

25 at 0.01 to 0.5% w/w of the formulation.

77. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate.

30 78. The method according to claim 74 wherein the preservative system

comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

79. The method according to claim 74 wherein the preservative system
5 comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

80. The method according to claim 74 wherein the preservative system
comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

10 81. The method according to claim 74 wherein the preservative system comprises
a preservative enhancing solubilizer.

82. The method according to claim 81 wherein the preservative enhancing
solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination
15 thereof.

83. A method for delivering an immune response modifier (IRM) to a dermal
surface, the method comprising the steps of:

selecting a formulation comprising:

- 20 (a) an immune response modifier selected from imidazonaphthyridine
amines, imidazotetrahydronaphthyridine amines, and
thiazolonaphthyridine amines;
- (b) a fatty acid;
- (c) a hydrophobic, aprotic component miscible with
the fatty acid and comprising a hydrocarbyl group of 7 or more carbon
atoms; and

25 applying the selected formulation to the dermal surface.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/38190

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K31/4745	A61K31/4375	A61K31/4355	A61K31/4365	A61K31/437
	A61K47/00	A61K47/26	A61K47/36	A61K47/38	A61K47/44
	A61P17/00	A61P17/02	A61P17/12		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHOLLET J L ET AL: "DEVELOPMENT OF A TOPICALLY ACTIVE IMIQUIMOD FORMULATION" PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, NEW YORK, NY, US, vol. 4, no. 1, January 1999 (1999-01), pages 35-43, XP000900717 ISSN: 1083-7450 abstract page 36, column 1, paragraphs 3,4 page 40, column 2 -page 41, column 2, paragraph 2 page 42, column 2, paragraph 4 -page 43, paragraph 2</p> <p>—</p> <p style="text-align: center;">-/—</p>	1-3,7,8, 10-12, 18,22, 25, 27-29,41

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
22 April 2003	07/05/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Houyvet, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/38190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,Y	WO 02 46188 A (3M INNOVATIVE PROPERTIES CO ;MERRILL BRYON A (US); CROOKS STEPHEN) 13 June 2002 (2002-06-13) page 3, line 5 -page 7, line 10 page 26, line 9 -page 27, line 10	1-83

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 02/38190**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 22-41 and 65-83 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/38190

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